UNIVERSITY OF CALIFORNIA SAN DIEGO

Prevalence of prescription opioid use during pregnancy: Indication of use, duration of use, and description of maternal characteristics

A Thesis submitted in partial satisfaction of the requirements for the Master's degree

in

Public Health

by

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The Thesis of Katherina Angela Nardo is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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DEDICATION

The goal of public health is to improve health and wellbeing and prevent suffering of populations. I chose this field to help others, especially those who are most in need of help. This thesis is dedicated to Adeline Nardo, who embodied what it means to be generous, selfless, and to live a life of service. I am proud to carry out her unfulfilled dream of pursuing higher education, particularly in a field where I can be of service to others—something she taught me through example for 17 years.

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LIST OF ABBREVIATIONS

ACOG	The American College of Obstetricians and Gynecologists
APS	American Pain Society
BMI	Body mass index (weight [kg] / height^2 [m])
CDC	Centers for Disease Control and Prevention (of the Department of Health and Human Services, United States)
CSA	Controlled Substances Act 1971, 21 U.S.C. ch. 13 § 801 et seq.
DEA	United States Drug Enforcement Administration
ER	Emergency room
FDA	The Food and Drug Administration (of the Department of Health and Human Services, United States)
LMP	Last menstrual period
MME	Morphine milligram equivalent
MMWR	Morbidity and Mortality Weekly Report (of the Centers for Disease Control and Prevention
MoBa	The Norwegian Mother and Child Cohort Study
NA	No answer
NAS	Neonatal abstinence syndrome
NIDA	National Institute on Drug Abuse (of the National Institutes of Health, United States)
NIH	National Institutes of Health (United States)
NSAID	Nonsteroidal anti-inflammatory drug
OB/GYN	Obstetrician/gynecologist or obstetrics and gynecology

OR	Odds ratio
OTC	Over-the-counter drug (not requiring a prescription)
OTIS	The Organization of Teratology Information Specialists
RCOG	Royal College of Obstetricians and Gynaecologists (United Kingdom)
SAB	Spontaneous abortion
SES	Socioeconomic status
SIDS	Sudden infant death syndrome
TAB	Terminated abortion
TJC	The Joint Commission

LIST OF TABLES

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ABSTRACT OF THE THESIS

Prevalence of prescription opioid use during pregnancy: Indication of use, duration of use, and description of maternal characteristics

by

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Master's degree in Public Health

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Professor Gretchen Bandoli, Chair

Objective: Opioid prescription rates in North America have increased dramatically over the past two decades, but little is known about prenatal opioid use. The purpose of this study is to determine the prevalence of prescription opioid use among pregnant women in the U.S. and Canada, as well as the duration, timing, and indication of use and lastly, to provide a description of maternal characteristics of those who used opioids.

Methods: Data were collected between 2004-2018 from a prospective cohort of 1,035 women in the MotherToBaby Pregnancy Studies. Prescription opioid use was self-reported.

Results: Seven percent of women used any prescription opioids during pregnancy. Most used opioids to treat acute illnesses and injuries, during a single trimester of pregnancy. Similar proportions of use were found across Trimesters 1, 2, and 3. There were a higher proportion of women with low SES, low educational attainment, overweight or obese BMI scores, a history of miscarriages, a history of terminated pregnancies, tobacco use, and co-occurring health conditions among women who used prescription opioids than in women who did not.

Conclusion: Prescription opioids were used in pregnancy, and more often by women with other factors that increase the risk of adverse pregnancy outcomes. These findings support the call for additional research to examine the risk of adverse pregnancy or birth outcomes associated with prenatal opioid use.

CHAPTER 1: INTRODUCTION

Beginning in the mid-2000s, opioid-prescribing behaviors among U.S. health care providers steadily increased and ultimately peaked in 2012 with 81.3 prescriptions per 100 Americans—an equivalent of approximately 255 million prescriptions.[1,2] While there has been an overall decrease in prescribing practices (58.7 prescriptions per 100 Americans in 2017), select counties suffer disproportionate opioid burden.[1] As of 2017, approximately 17% of adults in the U.S. filled at least one prescription for an opioid.[2]

Like the general population, pregnant women experience chronic conditions and acute ailments that may warrant the use of opioid pain relievers. However, since opioid prescriptions increased in just the past two decades, evidence of opioid use in pregnant women has just started to emerge in the past few years with the majority focused on illicit opioids (heroin) or medication assisted treatments for opioid addiction (e.g. methadone). Like with any medication taken during pregnancy, it is crucial to evaluate the safety of opioid use for both the mother and fetus and the potential long-term outcomes that may be associated with prenatal opioid use. Clarifying the scope of prenatal prescription opioid use is an essential first step in understanding the public health impact of this trend.

The purpose of this research is to identify in a large cohort of pregnant women throughout the United States and Canada, the prevalence of prescribed opioid use during pregnancy, as well as the duration of use, timing of use (pregnancy trimester), indication(s) of use, and any maternal characteristics that may be associated with increased likelihood for use. By describing these factors, this study will inform the design of future research intended to understand how timing, dose, and duration of use, as well as underlying medical conditions, contribute to reported adverse perinatal outcomes.

CHAPTER 2: LITERATURE REVIEW

2.1 Background

Opioid is an all-encompassing term to describe substances either derived from opium naturally found in poppy plants or a combination of both natural opium and a mixture of chemicals or other synthetic ingredients.[3] Examples of natural opioid analgesics—also referred to as 'opiates'—include morphine and codeine.[4,5] Common semi-synthetic opioids include oxycodone, hydrocodone, hydromorphone, and oxymorphone, while methadone, tramadol, propoxyphene, and fentanyl are classified as fully synthetic opioid analgesics.[4,5] Many common prescription opioid brands, including Vicodin® (hydrocodone bitartrate and acetaminophen), Percocet® (oxycodone and acetaminophen), Tylenol #3® and #4® (codeine containing acetaminophen), and Ultracet® (tramadol hydrochloride and acetaminophen), contain both opioids as well as other non-opioid pain relievers such as acetaminophen, aspirin, and ibuprofen.[5] Prescription opioids can be taken in several different forms, including tablets, capsules, skin patches, liquid (to be consumed orally or intravenously), nasal sprays, and "lollipops" (dissolvable substance on a stick, to be taken orally).[6]

Opioids relieve pain and relax the body by activating opioid receptors that release dopamine and inhibit the brain from receiving pain signals.[3,5] While they are mainly used to treat moderate to severe pain, opioids have also been effective as cough suppressants, diarrhea relievers, and sleep disorder treatments.[6] The Centers for Disease Control and Prevention (CDC) recognize several side effects from opioids including constipation, nausea, vomiting, dry mouth, fatigue, dizziness, depression, confusion, lowered testosterone, itching, and sweating.[7] Opioid use can lead to tolerance (needing more frequent and/or higher doses to relieve pain) and dependence that results in physical withdrawal symptoms when medication is stopped.[7]

In the United States, the Controlled Substances Act (CSA) requires all drugs to be categorized within one of five schedules based on their ability to serve a medical purpose, whether they can be misused or abused, their potential for creating dependence or addiction, and overall safety.[6] According to the 2017 Drug Enforcement Agency (DEA) Resource Guide, the common opioids, morphine, oxycodone, hydrocodone, hydromorphone, propoxyphene, codeine, and fentanyl, are considered "Schedule II Narcotics," due to their high potential for abuse and for severe physical and psychological dependence.[6] The term 'narcotic' describes opioids from a legal perspective and does not denote scientific meaning.[5] However, unlike the largely illicit group of drugs in the Schedule I class, opioids provide a necessary medical purpose.[6]

2.2 Prescription Opioid Trends in the U.S. & Canada

The CDC estimates 43% of American adults experience some kind of pain (i.e. chronic, acute, episodic, etc.) involving the musculoskeletal system alone (e.g. back pain, headaches, arthritis, etc.).[8] Results from the 2012 National Health Interview Study showed 11.2% of adults report experiencing pain daily.[8] In an attempt to tackle the unaddressed pain plaguing Americans, the American Pain Society (APS) campaigned in the mid-1990s for "pain" to be officially considered a "5th vital sign" in addition to the four other standard vital signs: body temperature, blood pressure, heart rate, and respiratory rate.[9,10] By the early 2000s, this standard was widely accepted and ultimately put into practice, largely due to the Joint Commission's (TJC) "published standards for pain management in 2000."[11] Along with a political shift in health care standards, there was a simultaneous boom in opioid availability due to increased pharmaceutical development of the late 1990s and early 2000s.[11] These two concurrent factors

are considered the impetus for the large spike in opioid prescribing that ultimately peaked in the mid 2010s and arguably has led to the current opioid epidemic in the United States.[11]

In 2017, there were 191 million opioid prescriptions filled in the United States, which were prescribed to about 17% of the population for an average of 18 days per prescription.[2,7] In Canada, an estimated 13% of the population (approx. 4.6 million Canadians) received prescriptions for opioids in 2018.[12] Of those who received an opioid prescription, 17.6% received an opioid prescription for long-term use.[12] More than half (62.8%) of these patients prescribed opioids for long-term use were prescribed "strong" opioids (defined as "all fentanyl, hydromorphone, morphine, and oxycodone products") typically reserved for severe pain associated with surgery or cancer.[12] Despite a slight decrease in prescribing in both the U.S. and Canada, the CDC recognizes that as of 2017, "the amount of opioids in morphine milligram equivalents (MME) prescribed per person is still around three times higher than it was in 1999."[2] In the U.S., prescribing rates are also disproportionately higher for people who are unemployed, uninsured, have arthritis, have a disability or are white.[2] Unsurprisingly, with the increased use of opioids in general, there has been an increase in the misuse of opioids as well.[11,13]

2.3 Opioid Misuse, Opioid Epidemic, and Response

Prescription opioid use is considered 'misuse' if it is taken in a way that it was not intended per the prescribing physician (i.e. different method of consumption, different dose, taking for longer than prescribed, etc.), if it is taken by someone other than the patient who received the prescription, or if it is taken for recreational purposes.[3] In 2016, 11.5 million Americans admitted to misusing prescription opioids, though the actual amount is likely greater.[7] Opioids inherently produce "euphorigenic or pleasurable effects" as a result of opioid receptors

binding endorphins, which involves the brain's reward system.[5] The probability that someone will use opioids a year after being prescribed increases abruptly after the five days of use, suggesting that physical dependence can occur less than a week after initiation of use.[14] The CDC also recommends that opioids given for acute pain typically requires a prescription of three days or less and very rarely requires prescriptions longer than seven days.[6] The National Institute on Drug Abuse's (NIDA) Prescription Opioids and Heroin Research Report Series from 2018 concluded, "prescription opioid use is a risk factor for heroin use."[15] The pooled data from 2002-2012 showed an incidence of heroin use 19 times higher for those who had "prior nonmedical pain reliever use" than the general population.[15] While only a small amount of people who use prescription opioids will later use heroin, 80% of heroin users claimed to have used prescription opioids before ever using heroin.[15] It is important to note that the report does not clarify whether the prior prescription opioid use was lawfully prescribed nor whether it was being misused.

Of the 42,000 opioid overdose deaths in 2016 throughout the U.S., 40% were estimated to be from prescription opioids.[16] In 2017, the number of overdose deaths increased to nearly 48,000 people.[17] The opioid epidemic of the past decade has led to a substantial reduction in prescribing rates and an overall change in both the public and health care providers' attitudes regarding the use of opioids as pain relievers. In 2019, the Canadian Pharmacists Association recommended that Canadian law be changed to require a prescription for any medication containing codeine.[18] Currently, medications containing acetaminophen with codeine are over the counter (OTC) in all but one Canadian province.[19]

The CDC also responded to the opioid crisis by publishing a set of evidence-based recommendations for prescribing opioids for chronic pain in 2016.[8] In this guideline, chronic pain is defined as "pain conditions that typically last >3 months or past the time of normal tissue

healing" and long-term opioid use is defined as "use of opioids on most days for >3 months."[8] Because of the risks associated with long-term opioid use, they recommend "nonpharmacologic therapy and nonopioid pharmacologic therapy" as the primary treatment options for people experiencing chronic pain.[6] Opioids should only be prescribed in these cases if the benefits will outweigh the risks.[6] If opioids are prescribed, they should be given at the lowest effective dosage, should be immediate-release rather than extended-release, and should be combined with nonpharmacologic and/or nonopioid pharmacologic therapies.[6] To avoid accidental overdose, providers should avoid prescribing concurrently with benzodiazepines.[6] The guideline also emphasizes the importance of screening patients for current addiction and to avoid prescribing any opioids to those with a heightened chance of developing addiction.[6]

Despite a modest decline in opioid prescriptions and increased caution among prescribers in the U.S. and Canada, providers continue to prescribe opioids to pregnant women. Misuse of opioids during pregnancy also mirrors the rise in misuse among the general population during the same time. Among women who have delivered in hospitals, the number who were misusing opioids increased by 127% between 1998 and 2011.[20] Currently, there is far less evidence describing prescription opioid use among pregnant women than there is describing opioid abuse and addiction among pregnant women.

2.4 Emerging Evidence: Birth Complications and Fetal Outcomes

While more evidence on current prescription opioid use among pregnant women in the U.S. and Canada is needed, the existing evidence on pregnant women with opioid abuse disorders has allowed for the emergence of several studies on pregnancy and fetal outcomes that were correlated with prenatal opioid use. For example, in a nationally representative pediatric

inpatient database of hospital discharge summaries, antepartum maternal misuse/dependency at the time of delivery increased 1.19 to 5.63 per 1,000 hospital births per year between 2000 and 2009.[21] With the increase in maternal opioid abuse in the past decade has also been an increase in neonatal abstinence syndrome (NAS).[21] NAS occurs when the fetus develops opioid dependency in the womb and experiences withdrawal once born.[21] From the same pediatric inpatient database, incidence of NAS also increased from 2000-2009, rising from 1.20 to 3.39 per 1,000 hospital births.[21] The study's investigators also report that mothers with diagnosis of opioid dependence or misuse were more likely to be Medicaid recipients than mothers that did not use opioids during pregnancy.[21]

Several of these authors also conducted a second analysis to assess incidence and geographic distribution of NAS in the U.S. for the years following those in the first investigation. Between 2009 and 2012 there was an additional increase in incidence of NAS: 3.4 to 5.8 per 1,000 hospital births respectively.[22] Both studies found similar associations between NAS and birth complications. Babies born with NAS were more likely than their non-NAS counterparts to have low birth weight, respiratory problems, feeding difficulties, seizures, jaundice, and sepsis.[21,22] Although NAS is a transient condition, the long-term consequences of prenatal opioid exposure have not been well studied.

While heavier and more consistent use of opioids during pregnancy is most often associated with NAS, opioids can cross the placental and blood brain barriers, meaning that the fetus may receive exposure to the drug regardless of how heavily the mother uses. The biological effects of opioid exposure in the womb, if any, are not well understood. However, early explorations of outcomes have shown that opioid use during pregnancy is a risk factor for pregnancy complications and adverse birth outcomes.[3,8,23-29] Results from these studies have

demonstrated that maternal opioid use was associated with increased risk of severe pregnancy complications, including spontaneous abortion,[3,8,23] membrane ruptures,[23,24] preeclampsia,[23] placental abruption,[23] and Cesarean delivery.[24,25] Maternal opioid use was also associated with risk of detrimental birth outcomes such as premature labor or birth,[8,23,24,26-28] low birth weight,[3,26,27] congenital abnormalities,[23,26,27] admission to neonatal care unit,[24] worse Apgar scores,[24] neonatal sepsis,[24] fetal intracranial hemorrhage,[24] and fetal or infant death (including stillbirth,[27,28] sudden infant death syndrome (SIDS),[29] and death from all causes[23,24,29]). Many of these studies only included women with substance use disorders rather than all women who were prescribed opioids. This distinction is crucial since women with substance use disorders may be using opioids more frequently and at higher doses than those prescribed and may also be abusing other substances that contribute to these same outcomes. Some of these studies also had relatively small samples and were only focused on the biological effects of one type of opioid. Despite the lack of large-scale, generalizable results, organizations that oversee maternal and child health explicitly listed opioid use as a risk for these complications.[8,28,30,31] This decision was likely made to deter the prescription of opioids to pregnant women due to the seriousness of the outcomes exhibited in these early studies.

Emerging evidence suggest that opioids taken just before conception or during the early weeks of pregnancy impact a fetus's risk of some birth defects. In a case-control study of mothers of babies with and without particular birth defects, there was a statistically significant association between opioid use during pregnancy and risk of several heart defects, spina bifida, and gastroschisis.[32] Another case-control study compared mothers of babies with neural tube defects (cases), mothers of babies with another kind of malformation (first control group), and mothers of babies with no defects (second control group) between 1998 and 2010.[33] The

researchers found that mothers of children with neural tube defects were more likely to report using opioids during pregnancy than both the malformed control group (OR 1.9) and the non-malformed control group (OR 2.2).[33] The associations were stronger when comparing those who had children with spina bifida specifically (OR 2.2 and 2.5, respectively).[33] The most commonly reported opioids among users in this study were codeine, oxycodone, and hydrocodone.[33]

Despite these early findings from case-control studies, there is mixed evidence about whether opioids are teratogenic drugs. A large population-based cohort study found no differences in the malformation rate between fetuses who were exposed to codeine in the womb and those who were not exposed.[25] A 2017 systematic review determined the quantity and quality of the existing studies to be insufficient for verifying a clear association between opioid use during pregnancy and congenital malformations.[20]

A Morbidity and Mortality Weekly Report (MMWR) published in 2019 highlights an ecologic link between rates of opioid prescriptions and gastroschisis prevalence.[34] Overall, gastroschisis prevalence has increased by 10% from 2006-2010 to 2011-2015 in the United States.[34] In this timeframe, the prevalence of gastroschisis was 1.6 times higher in high-prescribing counties (5.1 per 10,000 live births) and 1.4 times higher in moderate-prescribing counties (4.6 per 10,000 live births) than in low-prescribing counties (3.2 per 10,000 live births).[34] However, there are several limitations in this study including the fact only 20 states are included, possible confounders are not addressed in the analysis, and possible biological mechanisms linking the exposure and outcome are not known.

More recently, case-control studies examining an association between prescription opioid use during pregnancy and learning disabilities, developmental disorders, and autism have been conducted. A study using Tennessee Medicaid and birth certificate data linked to data from the

Tennessee Department of Education examined children between the ages of 3-8 years old.[35] Investigators matched 1,815 children born with NAS with 5,441 children without.[35] After controlling for potential confounders, such as maternal education, perinatal smoking, low birth weight, preterm birth, and NICU admission, children born with NAS were significantly more likely to "be referred for a disability evaluation" (19.3% vs. 13.7%, respectively), "meet criteria for a disability," (15.6% vs. 11.4%, respectively), and "require classroom therapies or services" (15.3% vs. 11.4%, respectively).[35] A 2019 case-control study comparing children with autism spectrum disorder only, children with a developmental delay/disorder (no autism features) only, children with either autism spectrum disorder or developmental delay/disorder with autism features, and population controls (total of ~2,800 cases and ~1,500 controls) also found an association with opioid use immediately before pregnancy and risk of having a child with hindered developmental outcomes.[36] The authors found, after adjusting for confounders, having a "preconception opioid prescription" was associated with risk of having a child with autism spectrum disorder (OR 2.43) and having either autism spectrum disorder and/or a developmental disorder with autism features (OR 2.64).[36] Like the majority of other studies, participants received prescriptions for hydrocodone, oxycodone, and codeine prescriptions more frequently than other types of opioids.[36]

While more studies are needed, those that exist support the CDC's "Pregnancy and Opioid Pain Medications" factsheet suggesting that these studies have yielded enough evidence to justify caution when prescribing opioids to women who are or may become pregnant.[28] The factsheet lists "neonatal opioid withdrawal syndrome, neural tube defects, gastroschisis, congenital heart defects, stillbirth, and preterm delivery" as possible risks when taking opioids during pregnancy.[28]

2.5 Current Recommendations

The American College of Obstetricians and Gynecologists (ACOG) produced a set of official recommendations for obstetrics/gynecology (OB/GYN) care in 2017. The committee, which included input from the American Society of Addiction Medicine, reaffirmed their recommendations in 2019. As with health care providers of any specialty, it is recommended that patients are screened for opioid use and opioid use disorders.[30] The guidelines also suggest hesitancy when prescribing opioids for pregnant patients who experience chronic pain.[30] The preferred pain treatments include physical therapy, exercise, behavioral methods, or non-opioid medications.[30] Even patients who are not pregnant but are of reproductive age should be informed about how if she were to become pregnant, the treatment plan may change depending on the risks and benefits for that individual.[30] Before prescribing opioids, the ACOG recommends the OB/GYN: 1) discuss with the mother the costs/benefits of using opioids during pregnancy, 2) determine the patient's substance abuse history, and 3) "ensure that opioids are appropriately indicated."[30] Despite their strict parameters for prescribing opioids to pregnant women, the ACOG notes that "acute pain" should not be left untreated in pregnant patients simply due to a physician's "concern for opioid misuse or NAS."[30]

In 2018, the Royal College of Obstetricians and Gynaecologists (RCOG) published recommendations that corroborate the claims that ACOG produced a year earlier. While both organizations discourage providers from withholding treatment for their pregnant patients, the RCOG actually claims that by doing so, the patient could develop anxiety and depression, which can have negative impacts on the pregnancy.[31] The RCOG reports acetaminophen is the first pharmacological choice for treating mild to moderate pain because it can be used during any trimester without fear of birth defects.[31] Often, if women are experiencing pain that cannot be

relieved by acetaminophen, such as severe migraines, autoimmune disease pains, etc., nonsteroidal anti-inflammatory drugs (NSAIDs) can be prescribed.[31] However, if providers are to prescribe an NSAID, it should be at the lowest dose, for the shortest duration, and only during the first 30 weeks of pregnancy.[31] Similarly, opioids should only be prescribed to pregnant patients if acetaminophen and other remedies fail to alleviate the pain.[31] The RCOG does not condemn the prescription of opioids after 30 weeks, but suggests the smallest dose and shortest duration possible to avoid fetal respiratory depression.[31] Still, the RCOG urges providers to address pain in pregnant patients using non-pharmacological treatments first.[31] The ideal pain alleviation methods include relaxation and rest, using heat and ice, acupuncture, massage, physical therapy, and exercise.[31]

2.6 Study Objectives

To date, our understanding of prescription opioid use in pregnancy primarily derives from Medicaid studies,[37,38] which rely on administrative claims and over-represent minority and low-income women. Administrative claims, which describe the filling of prescriptions, may diverge from actual use, particularly for medications taken 'as needed.' The profile of women in the U.S. or Canada who use prescription opioids in pregnancy, particularly outside of the public insurance system, has not been identified. Without adequate existing evidence, we also lack the ability to make informed analytical adjustments and contextualization of any findings. This is particularly pronounced in studies of offspring outcomes, where the underlying maternal characteristics and medical comorbidities of women using prescription opioids in pregnancy are often unknown, and therefore residual confounding by these factors is of concern. Therefore, this analysis aims to describe, from a relatively healthy sample, the type of woman that uses

prescription opioids during pregnancy, as well as why the opioid was prescribed, when and for how long the opioid they were taken, and which types of opioids were prescribed. This initial descriptive study aims to lay the necessary groundwork for forthcoming research examining the safety of perinatal opioid exposure and long-term effects for both the mother and the fetus.

CHAPTER 3: METHODS

3.1 Data Source

3.1.1 Background

The nonprofit organization, Organization of Teratology Information Specialists (OTIS), conducts a variety of maternal and child health studies in conjunction with their "MotherToBaby" pregnancy counseling service. The counseling service is provided at several sites across the U.S. and Canada where women can ask experts about the risks associated with certain exposures during pregnancy, such as medications, environmental exposures, infections, maternal health conditions, herbal products, cosmetics, and so on.[39-41] The MotherToBaby service also comprises research teams that conduct observational studies on these types of exposures during pregnancy and breastfeeding to examine associations with maternal, child, and pregnancy outcomes.[39] MotherToBaby research studies are funded through grants from the CDC, the Health Resources and Services Administration at the U.S. Department of Health and Human Services,[42] pharmaceutical companies for post-marketing surveillance studies, and grants through the National Institutes of Health.

3.1.2 Study Design & Data Collection

Pregnant women across the U.S. and Canada are recruited to participate in a MotherToBaby Pregnancy Study in several ways, such as through referral from their physician or through direct advertisements.[40,41,43] The most common recruitment approach is referring the women who call the MotherToBaby counseling service to the Pregnancy Studies. [40,41,43] There were 4,233 women who were enrolled prior to 20 weeks gestation in a MotherToBaby research study between 2004-2018. Informed consent was obtained from all enrolled participants. Immediately after enrolling, researchers conducted a semi-structured one-on-one telephone

interview. In addition to this baseline interview, participants were interviewed up to three more times (depending on their gestational age at enrollment) at ~24 weeks gestation, ~32 weeks gestation, and after birth.[43] Data collected via interviews include demographic information, medical histories, and information on exposures and outcomes. The researchers conducting these interviews were trained both directly by the supervisors as well as through observation of live interviews and could not conduct an interview alone until the study supervisor deemed it appropriate.[40]

3.2 Measures

3.2.1 Exposure

Prescription opioid exposure was defined as any use of a prescription opioid that has been prescribed specifically to that participant by a licensed health care provider. Participants reported opioid use through daily diaries. Based on the participant's last menstrual period (LMP), which was used to define the beginning of the pregnancy, data were then recoded to display "any use (yes/no)" by week of pregnancy (ranging from 1 week before LMP up to 42 weeks gestation or delivery depending on which came first). Exposure to more than one opioid on a given day or week were not double-counted as the variable was coded as binary (yes, used or no, have not used).

Women also reported the type or brand of opioid used as well as the indication for use (multiple indications could be reported for each exposure or across exposure periods). These indications were separated into chronic and acute categories. Chronic categories include chronic pain, chronic migraines, and autoimmune disease(s). Acute categories include acute illness or injury, surgery or procedure, cold or flu, and ER visit (specific indication unknown). Opioid

classification was separated by type of opioid based on either explicit report or by recoding the specific brand that was reported.

3.2.2 Covariates

During the baseline interview, participants reported their age, race, ethnicity (Hispanic/Latina or not), whether their pregnancy was planned, prenatal vitamin use, parity, miscarriage history, terminated pregnancy history, and for multigravida women, whether there has been a paternity change prior to this pregnancy. Geographic data for participants included their state or province and country of origin, which were grouped into region based on the United States Census Bureau Regions and Divisions.[44] The "Northeast" region includes Maine, New Hampshire, Vermont, Massachusetts, Connecticut, Rhode Island, Pennsylvania, New York, and New Jersey. The "South" region includes the District of Columbia, Maryland, Delaware, Virginia, West Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Florida, Alabama, Mississippi, Arkansas, Louisiana, Oklahoma, and Texas. The "Midwest" region includes Ohio, Indiana, Illinois, Missouri, Kansas, Nebraska, Iowa, Michigan, Wisconsin, Minnesota, North Dakota, and South Dakota. The "Mountain" region included New Mexico, Arizona, Colorado, Utah, Nevada, Idaho, Wyoming, and Montana. Lastly, the "Pacific" region included Washington, Oregon, California, Hawaii, and Alaska. Because of the comparatively small number of Canadian participants in this sample, all Canadian provinces were grouped together under the category, "Canada."

Pre-pregnancy height and weight were used to determine pre-pregnancy body mass index (BMI). BMI was then categorized using the standardized BMI score chart into "underweight" (BMI <18.5), "normal weight" ($18.5 \leq$ BMI < 25), and "overweight or obese" (BMI > 25).[45] Highest education level and occupation were used to estimate Hollingshead socioeconomic

status (SES), with scores of 5-6 categorized as low SES.[46] Women also indicated whether they had previously been diagnosed with an autoimmune disease, asthma, depression, anxiety disorder, or other mental health disorder. Throughout the pregnancy, women reported antidepressant use, any tobacco consumption, last week of alcohol consumption, and first week of prenatal vitamin use. After birth, delivery method and gestational age at delivery (in weeks) were recorded.

3.3 Sample

For this study, all women in the MotherToBaby database were eligible if they had originally enrolled before their 20th week of gestation (n=4,161). To have complete capture of opioid use across gestation, this sample was restricted to only include women who had live births, excluding spontaneous abortions (n=238), terminated gestations (n=15), ectopic pregnancies (n=2), and stillbirths (n=17) to give all participants the same temporal window for potential exposure to allow for more comparable periods for exposure. Finally, multiple births (n=275), pregnancies lost to follow up/withdrew consent (n=241), and pregnancies that had not yet completed gestation at the time of analysis (n=360; categories not mutually exclusive) were removed, resulting in 3,291 women. Several of the MotherToBaby Pregnancy Studies were focused on women with particular conditions such an autoimmune disease or asthma.[47] To more accurately reflect the female population in the United States and Canada, prevalence of participants with an autoimmune disease and with asthma were randomly down sampled to reported population prevalence of 3% and 10% of the sample[48,49] respectively, bringing the sample total to 1,035 women.

3.4 Statistical Analysis

Maternal characteristics were stratified by opioid use status to examine the differences among those who did and did not use opioids during pregnancy. Counts and percentages were used for categorical variables and means and standard deviations were used for continuous variables. Proportions were given for indications for use and separated by indication category, as well as for type of opioid used separated by indication categories and overall number of reports. Counts of opioid use per U.S. state grouped into regions were examined for geographic variation.

Prevalence of opioid use was assessed by stage of pregnancy (before LMP, Trimester 1, Trimester 2, and Trimester 3) and by number of trimesters used (one, two, or all three trimesters). The variable "before LMP" was limited to 1 week before the participant's estimated first week of pregnancy. Trimester 1 included exposure from weeks 1-12, Trimester 2 included exposure from weeks 13-26, and Trimester 3 included exposure from weeks 27-42 of the pregnancy or delivery, whichever occurred first. Proportions were out of total number of participants who used opioids. To evaluate frequency of opioid use within each trimester, interquartile ranges and mean number of weeks used were reported. All data were analyzed using JMP® 14.1.0 software.[50]

CHAPTER 4: RESULTS

The demographic characteristics of the study population are presented in Table 1. Of the 1,035 women in this study, 67 (6.5%) reported any opioid use during pregnancy. The mean ages for women who had taken opioids and those who had not were approximately 33 years and 32.5 years, respectively. Both groups—those who used opioids and those who did not—were largely White (88% and 87%, respectively) and Non-Hispanic/Latina (88% and 87%, respectively). However, the proportion of women who had low SES and the proportion of women who were overweight or obese were each higher among those who had taken opioids than among those who did not (16% vs. 9% and 46% vs. 32%, respectively). On average, women who took opioids also had less education, with 16.5% having only a high school diploma or less, while only 8% of women who had not taken opioids completed only high school or less. The proportion of women who had earned a graduate-level degree was greater among women who had not taken opioids than among those that had (37.7% vs. 22.4%). Among opioid users, the proportions of reported comorbid conditions—autoimmune disease(s), asthma, depression, anxiety disorder, and other mental health disorders—were all about 1.5-1.6 times higher than the proportions in the non-user group. The proportion of any tobacco use was three times higher for women that used prescribed opioids than for those who did not, with 12% and 4% using tobacco, respectively.

In terms of pregnancy-related characteristics, women who used prescription opioids also more frequently reported having a history of one or more terminated pregnancies than women who did not use opioids during pregnancy (18% and 9.5%, respectively). The proportion of women whose pregnancy was unplanned and the proportion of women who had one or more changes in paternity between children were each 1.6 times larger for opioid-using women than the proportion for non-users.

Data on the timing and duration of opioid use are presented in Table 2. Percentages of women who took opioids during each stage of pregnancy were relatively similar. The number of trimesters used was far less similar with just 6.3% of opioid-using participants using an opioid during all three trimesters of pregnancy. Three quarters of opioid-using participants used during one of the three trimesters.

In Table 3, the number of weeks of opioid use was reported by pregnancy stage as well as by total duration of the pregnancy. Number of weeks women used opioids were relatively similar per trimester, ranging from no use in the 25% quartile to about 2 weeks used for each trimester in the 75% quartile.

Of the 67 participants who reported opioid use (see Table 4), there were 92 specific indications reported (29 chronic and 63 acute). The most frequently reported indication overall was acute illness or injury, which included musculoskeletal injuries, infections, kidney stones, acute abdominal pain, and dental-related pain. Slightly over half of the chronic indications were for migraine.

The types of opioids prescribed differed depending on whether they were prescribed for chronic or acute indications (see Table 5). For chronic indications, the most commonly prescribed opioid was hydrocodone (37%) followed by oxycodone and codeine (both 18.5%). The opioids for acute indications were more evenly distributed. Overall, hydrocodone (29%) and codeine (27%) were the most prescribed opioids. The least prescribed opioids were Fentanyl (2%) and propoxyphene (1%).

Table 6 displays the distribution of opioid use by geographic region. The vast majority of the 1,035 participants were United States residents. The region with both the fewest total participants and lowest percentage of opioid users was Canada, with only 4% of the 67 total

participants reporting opioid use. In the United States, the prevalence of opioid use by region ranged from 4.3% of Midwestern participants to 8.9% of the participants in the Pacific region.

CHAPTER 5: DISCUSSION

5.1. Summary of Findings

Because of the large number of opioids currently being prescribed in the United States and the potential for adverse birth outcomes associated with prenatal opioid use,[1,2] this study aimed to describe prescription opioid use among a prospective cohort of pregnant women. Specifically, this study analyzed prevalence of prescription opioid use, characteristics of mothers with prescription opioids during gestation, as well as timing, duration, and indication of use. Overall, in the sample of 1,035 pregnant women residing in the U.S. or Canada, approximately 6.5% reported any opioid use—as prescribed by their healthcare provider—during their pregnancy.

Women who used prescription opioids during pregnancy on average had less education, lower SES, were more likely to be overweight/obese, and more likely to be diagnosed with a comorbid condition (including autoimmune disease(s), asthma, depression, anxiety, and other mental health disorder(s)) than women who did not use opioids. They also had lower proportions of planned pregnancy and higher proportions of tobacco use during pregnancy, paternity change(s), prior spontaneous abortion(s), prior terminated abortion(s), and births via Cesarean delivery, compared to their counterparts.

5.2. Comparison to the Literature

To our knowledge, this is the first prospective cohort study to describe both prescription opioid use among a national sample of pregnant women in the U.S. and Canada as well as the maternal characteristics of those who used prescription opioids. However, there have been a few previous studies that have investigated similar trends among cohorts in different populations.

5.2.1. Prevalence of Prescription Opioid Use

Over the study period (2004-2018), 6.5% of women in our sample used prescription opioids at some point during their pregnancies. The prevalence of prescribed opioid use among pregnant women has varied considerably among different cohorts. For example, in a prospective cohort study that followed 1.1 million pregnant women enrolled in Medicaid in the U.S. between 2000-2007, 21.6% of participants "filled a prescription opioid during pregnancy."[37] Another Medicaid-enrolled cohort of 277,555 pregnant women in Tennessee found that between 1995-2009, 29% of the participants filled a prescription for an opioid.[38] In a study by Bateman et al., which followed 534,500 pregnant commercial insurance beneficiaries in the U.S. from 2005-2011, 14.4% of participants filled a prescription for opioids.[51]

A possible explanation for the difference in the percent of women prescribed opioids between the MotherToBaby cohort and these other cohorts could be because the data from these cohorts were based solely on information from insurance records, so it is unclear if this number accurately reflects the number of women who actually used the prescribed opioids after they were filled. The data from the MotherToBaby cohort consists of self-reported dates of use and reasons for use, decreasing the potential for exposure misclassification from reliance on claims data. Another reason opioid prescription was more common among these cohorts may have been because the dates of the study periods exactly coincided with the years when opioid prescription rates began increasing drastically in the general U.S. population, whereas our study period included years after there was an overall decrease in prescriptions in the wake of the opioid epidemic.[1,2,11,13] Finally, there is likely a selection bias in our study due to the types of women who have the time and resources to volunteer for a study relatively early in gestation and continue participation through gestation.

Similar studies have been conducted in Canada,[52] Sweden,[53] and Norway[25,54,55] and have reported proportions of perinatal opioid use far lower than the 6.5% found among our sample of women. The Canadian cohort study, which just included fee-for-service medical claims data from pregnant women residing in Manitoba, found that among the 175,174 pregnant women between 2001-2013, approximately 3-4% had used a prescription opioid per trimester.[52] In the Scandinavian studies, which utilized some of the largest national pregnancy and birth cohorts in the world, prevalence was even smaller. For example, of 102,995 women who gave birth in Sweden in 2007, just 1.4-1.8% per trimester had reported prescription opioid use.[53] A cohort study by Handal et al. used data from the Medical Birth Registry of Norway and the Norwegian Prescription Database between 2004-2008 and found that 3% of women were prescribed opioids at some point during pregnancy.[54] Data from the 51,679 pregnancies in the Norwegian Mother and Child Cohort Study (MoBa) found that prescription opioid use occurred in only 1.7% of pregnancies.[55] An earlier study using the MoBa data found that among 67,982 women between 1999-2006, 3.9% had used codeine specifically during pregnancy.[25] While these cohorts all reflect our sample more closely in terms of race, ethnicity, SES, and educational attainment, the large difference in prescription opioid rates for pregnant women is likely due to there being a much lower prevalence of prescription opioids in general in these countries compared to the United States.[56,57] This is especially true during the mid-2000's when most of these cohorts were examined. [56,57]

Not surprisingly, studies that more closely mirrored our sample demographics also yielded similar results for prevalence of prenatal opioid use. For example, in a cohort of 2,748 pregnant women from Massachusetts and Connecticut, 6% reported using opioids that were prescribed to them at some point during their pregnancy.[58] This cohort was the most similar to

ours in terms of race, ethnicity, and educational attainment compared to any of the other cohorts. This pattern suggests that our sample is likely an accurate estimation for only a subset of American and Canadian pregnant women.

5.2.2. Timing and Duration of Opioid Use

Regardless of the overall prevalence of prescription opioid use during pregnancy, nearly each of these studies reported similar trends of short-term use across each trimester. This was also true for the U.S. insurance-based cohorts[37,38,51] as well as the Scandinavian cohorts.[53-55] We also found that most participants had only taken opioids in one of the three trimesters. This too was consistent with the studies in Norway[25,54,55] and in the United States.[37,51]

5.2.3. Indications for Opioid Prescription

In this sample, opioids were most often prescribed for acute illnesses and injuries, followed by chronic migraines. Taken together, surgeries and procedures, cold and flu, and chronic pain constituted roughly a third of all reasons for prescription. Based on these findings, it is not surprising that the average number of weeks of opioid use was just one or two weeks per trimester and that the majority of women took opioids during only one of the three stages of pregnancy. This pattern of use in pregnant women differs from those found in the general population. For example, a 2018 retrospective cohort study of 1.3 million Americans over 14 years of age found that chronic pain conditions were the most common indication for people without a history of cancer diagnosis to receive opioid prescriptions.[59] A population-based cohort study conducted in Canada also published different findings in 2018.[60] The results of this study were that dental procedures, followed by postsurgical pain, were the two most frequently reported indications for first-time opioid prescriptions.[60] It is likely that because there is more hesitancy, both by providers and women, for using medications during pregnancy, the types of

reasons for opioid prescription differ in this population. Pregnant women may also be less likely to schedule surgeries or dental procedures during the course of their pregnancy (other than in the case of time-sensitive emergencies), which could account for the differences in indications between pregnant women and the general adult population.

The national cohort of Medicaid-enrolled pregnant women in the U.S. was the only study among these to also examine specific indications for use.[37] Their results showed that the most commonly reported indications for opioid prescriptions were abdominal pain (48.4%), low back pain (33%), headache syndromes (not including migraine) (13.3%), joint pain (11.2%), and migraines (7.9%).[37] The discrepancy in indications reported may have been due to the way that indications were grouped in our study. For example, in the MotherToBaby cohort, indications such as abdominal pain and back pain were common but were grouped into either "acute illness or injury" or "chronic pain" depending on the description of the indication and duration of the prescription. Among women in our cohort, migraines were also a far more common reason for opioid prescription than in the Medicaid-enrolled cohort.

5.2.4. Types of Opioids Prescribed

Of the 94 unique prescriptions reported in our sample, nearly three quarters were for hydrocodone (28.7%), codeine (26.6%), and oxycodone (18.1%). These three opioids were frequently reported as the most commonly prescribed to pregnant women in U.S. studies.[38,51,58] However, among Medicaid-enrolled pregnant women, both codeine and hydrocodone were reported as most prescribed, but oxycodone was not.[37] In the Norwegian cohort studies by Handal et al. and by Skovlund et al., codeine represented the overwhelming majority—94.5%[54] and 89.6%,[55] respectively—of opioids prescribed to pregnant women.

A minor difference between our results and others is that morphine and hydromorphone were used semi-frequently relative to the most (oxycodone, hydrocodone, and codeine) and least used opioids (fentanyl, tramadol, propoxyphene). The study by Bateman et al. showed morphine to be one of the least used opioids and did not have any reports of hydromorphone being prescribed.[51] However, our findings were similar to those of the study conducted among Massachusetts and Connecticut residents.[58] Smith et al. reported morphine and hydromorphone as the middle-used opioids, followed first by tramadol and then fentanyl.[58] Again, this similarity could be due to the fact our cohorts are the most demographically similar of those previously described.

Of note, tramadol is not technically an opioid by definition because it is not derived from opium[61] and thus may not have been measured in each of these studies. However, tramadol was included in our analysis because the drug acts like an opioid by targeting the same pain receptors as traditional opioids.[61] With that said, as of 2017 the U.S. Food and Drug Administration (FDA) officially has considered it a narcotic, specifically referring to it as an opioid.[62]

It is also worth noting that several of the opioids prescribed to participants in this study were in the form of combination medications that contain acetaminophen (such as Tylenol® products containing codeine) or another non-narcotic pain reliever, as is frequently done in the general population. These specific combinations have not been included in the analysis but rather were coded into the corresponding opioid category (i.e. which opioid ingredient was used). Including a wider definition of opioids may have contributed to a more heterogeneous report of opioid type. Also, there was a very low number of prescriptions for propoxyphene, which could have been due to the FDA's investigation of harms associated with the drug in the late 2000's and its ultimate removal from the U.S. market in 2010.[63]

Data on doses per opioid prescribed were not included in our analysis due to the lack of dose standardization across the many types of opioids. Morphine-milligram equivalent (MME) scores are the most used method for standardizing doses across the different types of opioids.[64,65] However, there is mixed evidence about whether these instruments are valid. Due to evidence showing unreliability and inconsistency with the MME conversion method, [64,65] dose was not included at this time. Dose was frequently excluded from the existing cohort studies as well.

5.2.5. Maternal Characteristics

While overall prevalence of prescription opioid use generally differed among cohorts, our descriptions of maternal characteristics more common in those who were prescribed opioids is largely consistent with the existing literature. For example, we found that almost half of women prescribed opioids had pre-pregnancy BMIs considered overweight or obese, whereas less than a third of non-users were overweight or obese. In the study by Skovlund et al., the proportion of Norwegian women who used opioids increased as BMI increased.[55] Similarly, Henriksen et al. also reported that codeine use during pregnancy was more common in people with an overweight/obese BMI.[25]

Another common finding was that educational attainment was frequently reported in relation to opioid use. We found that the group who were prescribed opioids had double the proportion of women with less than a high school degree than the group of participants that did not take opioids. Other studies reported that opioid use was less common with more education[25,55] and more common among those with less than a high school education.[50] Participants who had prior disabilities or medical conditions[38,55,58] (such as autoimmune diseases,[25] asthma,[25] and mental health disorders,[25,58] had reported consumption of tobacco (including smoking cigarettes)[25,55,58] or alcohol[25] during pregnancy, or had taken antidepressant

medication during pregnancy,[55,58] were also more likely to have received an opioid prescription during pregnancy. Other than alcohol use during pregnancy, each of these maternal factors were also more common among those who were prescribed opioids in our sample.

5.2.6 Geographic Distribution

Findings from this study show a relatively small geographical difference in the prevalence of prenatal opioid use proportions compared to the cohort of Medicaid-enrolled pregnant women that had "substantial regional variation" for the proportion of women who fill an opioid prescription depending on their home state.[37] The prevalence ranged from 9.5% to 41.6% with the highest proportions in Utah, Idaho, New Hampshire, Wyoming, and Tennessee. However, this study population only included women on Medicaid and used data collected between 2000 and 2007, which was before local, state, and national policies were implemented to reduce the overall prescription of opioids.

A 2017 NIH report showed that opioid overdose death rates in the U.S. varied greatly across states.[13] The highest rates of opioid overdose deaths occurred in Maine, New Hampshire, Massachusetts, Maryland, District of Columbia, West Virginia, Ohio, and Kentucky, and the very lowest rates were in California, Texas, and Hawaii.[13] These rates do not correspond with the proportions of maternal opioid use from the present study, which found higher rates to be in "Pacific" states (including California and Hawaii) and lower rates in the "Midwest" states (including Ohio) and "South" states (including Maryland, District of Columbia, West Virginia, and Kentucky). However, there was also a large number of states for which there was no enrollment, so the distribution may look different in reality. Opioid-related overdose deaths are also not an ideal comparison with prescription opioid use among pregnant women. However,

most of the existing cohort studies in the U.S. and Canada[38,51,52,58] either could not or did not measure national geographic distribution of perinatal prescription opioid use.

5.3 Strengths

One strength of this study is the large, prospectively collected sample of over 1,000 women. This is especially important when looking at opioid use, which typically encompasses such a small portion of the population. Additionally, the original group of eligible participants was down-sampled to better reflect the distribution of autoimmune disease of the U.S. and Canadian populations. Due to the nature of telephone-based interviews, the participants may have been more comfortable providing honest and detailed responses. Further, this analysis captures opioids as taken, as opposed to opioids as prescribed, which can be significantly different, and limits inference possible from large administrative claims database studies such as Medicaid.

5.4 Limitations

Several limitations must be considered when interpreting these findings. First, the recruitment methods lend themselves to introducing two types of selection bias. For example, because some women were recruited online and/or through advertisements, volunteer bias may skew the sample away from the general population that was aimed for. Women with more free time, who may be more trusting of medical advice, or who do not feel they need to hide socially undesirable behaviors may be more willing to volunteer. Second, the majority of women enrolled were made aware of the studies after calling experts to obtain information during pregnancy. These women are actively seeking health information and may be healthier than the general

population. Also, the sample differed from the general population of pregnant women in North America by race, ethnicity, geography, socioeconomic status, and education. Therefore, these results may not be generalizable to all pregnant women. There is also some risk for recall bias due to the self-report data collection methods. The data from the present study did not include participant zip code, so participants were unable to be coded as residents of either rural or urban areas. This could be an important addition to future studies because early evidence has found that between 2004-2013 in the U.S., maternal opioid use "increased disproportionately in rural counties…relative to urban counties."[66]

5.5 Conclusions

Among the women in the MotherToBaby cohort, those who use opioids during pregnancy differed from those who did not use opioids on the basis of SES, educational attainment, BMI, comorbid health conditions, and several different pregnancy characteristics and outcomes. Reassuringly, most women used an opioid during one or two different weeks of the pregnancy during just one trimester of the pregnancy. The most common reason for opioid use included acute illnesses and injuries.

The next step in our research will be to examine the actual birth outcomes for women in this sample. Recent changes in opioid prescribing behavior among health care providers warrant continued study of prevalence among pregnant women over the next decade. Given that this study population was down-sampled to accommodate for the oversampling of women with autoimmune diseases and asthma that were in the original dataset and that women with these conditions may be more likely to use opioids than the general population, another analysis could

examine if they are also more likely to be prescribed opioids during pregnancy as well as corresponding birth outcomes.

Additional studies with a more generalizable sample could greatly contribute to the existing literature on this topic. For example, because perinatal opioid use may impact whether a woman has a live birth,[8,23,24,27-29] similar analyses could be performed to include both successful and unsuccessful pregnancies. It is clear from the literature that researchers have only begun to explore the risks of negative outcomes for mothers and children exposed to opioids during pregnancy. While only 6.5% took opioids during pregnancy, when applying that proportion to the number of pregnancies in the U.S. and Canada per year (approximately 6.3 million[67] and over 380,000[68]) hundreds of thousands of pregnant women (and their children) will be exposed to opioids during pregnancy. Therefore, it is undoubtedly important to determine the safety of opioid use during pregnancy and the risks of pregnancy complications, adverse birth outcomes, and long-term consequences for mother and child.

APPENDIX

Table 1: Maternal characteristics by prescription opioid use exposure category (N=1,035) from women enrolled in MotherToBaby pregnancy study between 2004-2018

Characteristics	**No Opioid Use N= 968 (93.5)**		**Any Opioid Use N=67 (6.5)**	
Age (years), mean (±SD)	32.51	(±5.03)	33.25	(±4.54)
Race, N (%)				
White	843	(87.1)	59	(88.1)
Black	45	(4.7)	3	(4.5)
Asian	50	(5.2)	3	(4.5)
Pacific Islander	1	(0.1)	–	–
Indian/Native American	10	(1.0)	1	(1.5)
Other	17	(1.8)	1	(1.5)
NA[a]	2	(0.2)	–	–
Ethnicity, N (%)				
Hispanic/Latina	121	(12.5)	8	(11.9)
Non-Hispanic/Latina	845	(87.3)	59	(88.1)
NA	2	(0.2)	–	–
Highest education level, N (%)				
Less than 9th grade	3	(0.3)	–	–
Junior high school (9th)	8	(0.8)	3	(4.5)
Some high school (10th or 11th)	10	(1.0)	2	(3.0)
High school graduate	57	(5.9)	6	(9.0)
Some college	159	(16.4)	18	(26.9)
College or university graduate	366	(37.8)	23	(34.3)
Post-college graduate	365	(37.7)	15	(22.4)
SES[b], N (%)				
Low SES	88	(9.1)	11	(16.4)
High SES	859	(88.7)	56	(83.6)
NA	21	(2.2)	–	–
Pre-pregnancy BMI[c], N (%)				
Underweight (<18.5)	40	(4.1)	2	(3.0)
Normal (18.5 – 24.9)	613	(63.3)	33	(49.3)
Overweight/Obese (≥25)	308	(31.8)	31	(46.3)
NA	7	(0.7)	1	(1.5)

Table 2: Maternal characteristics by prescription opioid use exposure category (N=1,035) from women enrolled in MotherToBaby pregnancy study between 2004-2018

Characteristics	**No Opioid Use N= 968 (93.5)**		**Any Opioid Use N=67 (6.5)**	
Autoimmune disease(s)	28	(2.9)	3	(4.5)
Asthma	94	(9.7)	10	(14.9)
Depression	180	(18.6)	15	(22.4)
Anxiety disorder(s)	98	(10.1)	11	(16.4)
Other mental health disorder(s)	53	(5.5)	6	(9.0)
Antidepressant medication use	69	(7.1)	7	(10.4)
Any tobacco use	37	(3.8)	8	(11.9)
Prenatal vitamin use	940	(97.1)	66	(98.5)
1st week prenatal vitamin use (gestational week), (mean±SD)	-7.30	(±43.24)	-5.32	(±34.28)
Last week used alcohol, N (%)				
Never used	477	(49.3)	35	(52.2)
LMP – week 4	320	(33.0)	22	(32.8)
Week 5 – week 34	92	(9.5)	8	(11.9)
Week 35-40	79	(8.2)	2	(3.0)
SAB[d] History, N (%)				
None	717	(74.1)	44	(65.3)
1 or more SABs	251	(25.9)	23	(34.3)
TAB[e] History, N (%)				
None	876	(90.5)	55	(82.1)
1 or more TABs	92	(9.5)	12	(17.9)
Planned Pregnancy, N (%)				
Planned	753	(77.8)	44	(65.7)
Unplanned	214	(22.1)	23	(34.3)
NA	1	(0.1)	–	–
Paternity change, N (%)				
None	766	(79.1)	53	(79.1)
1 or more changes	114	(11.8)	13	(19.4)
NA	88	(9.1)	1	(1.5)

Table 3: Maternal characteristics by prescription opioid use exposure category (N=1,035) from women enrolled in MotherToBaby pregnancy study between 2004-2018

Characteristics	**No Opioid Use N= 968 (93.5)**		**Any Opioid Use N=67 (6.5)**	
Delivery method, N (%)				
Vaginal delivery	699	(72.2)	45	(68.2)
Cesarean delivery	266	(27.5)	21	(31.8)
NA	3	(0.3)	1	(1.5)
Gest. age delivery (wks)[f], mean (±SD)	39.20	(±1.76)	38.63	(±3.27)
Parity, mean (±SD)	0.75	(±0.98)	1.16	(±1.18)

[a] NA, no answer
[b] SES, socioeconomic status (High is Hollingshead categories of 1-3, low is categories 4 or 5)
[c] BMI, body mass index (weight divided by height^2)
[d] SAB, spontaneous abortion
[e] TAB, terminated abortion
[f] Participants missing from no-opioid use category (n=4) and opioid use category (n=1)

Table 4: Prevalence of prescription opioid use by trimester (2004-2018) and by cumulative trimesters

	Used Prescription Opioids (Y/N)	% of Total Opioid Users (N = 64[a])
Pregnancy Stage[b]		
Before LMP	9	(14.1)
Trimester 1	26	(40.6)
Trimester 2	29	(45.3)
Trimester 3	29	(45.3)
Number of Trimesters Used		
1 trimester	48	(75.0)
2 trimesters	12	(18.8)
3 trimesters (all)	4	(6.3)

[a] 3 participants did not report dates of opioid use

[b] LMP, last menstrual period; Trimester 1, gestational weeks 1-12; Trimester 2, gestational weeks

Table 5: Number of weeks used a prescribed opioid at least once by trimester and by cumulative pregnancy duration (average and interquartile range)

	Mean	(SD)	Median	Q1	Q3
Total Duration	5.75	(±8.44)	2.0	1.0	6.0
Trimesters					
Trimester 1	1.56	(±3.10)	0.0	0.0	1.75
Trimester 2	2.23	(±4.00)	0.0	0.0	2.0
Trimester 3	1.81	(±3.08)	0.0	0.0	2.0

Table 6: Indications for opioid prescription use by chronic and acute indication

	Indications Reported N = 92[ab]	**Indications by Use Category (%)**	**Indications by Total Reports (%)**
Chronic Indications	**29**	**(100.0)**	**(31.5)**
Chronic Pain	9	(31.0)	(9.8)
Chronic Migraines	15	(51.7)	(16.3)
Autoimmune Disease	5	(17.2)	(5.4)
Acute Indications	**63**	**(100.0)**	**(68.5)**
Acute Illness/Injury	41	(65.1)	(44.6)
Surgery/Procedure	10	(15.9)	(10.9)
Cold/Flu	10	(15.9)	(10.9)
ER Visit (Reason unknown)	2	(3.2)	(2.2)

[a] 2 prescriptions did not have a corresponding indication reported

[b] Of the 67 participants who used opioids, there were 94 separate prescriptions reported

Table 7: Prevalence of different types of prescribed opioids by indication category (acute or chronic indications) and by total prescriptions

	Total Prescriptions N= 94 (100.0)		**Prescriptions per Acute Indication N= 65[c] (100.0)**		**Prescriptions per Chronic Indication N= 27[c] (100.0)**	
Opioid Classification						
Morphine[a]	11	(11.7)	8	(12.3)	2	(7.4)
Hydromorphone	8	(8.5)	7	(10.8)	1	(3.7)
Hydrocodone	27	(28.7)	17	(26.2)	10	(37.0)
Oxycodone	17	(18.1)	12	(18.5)	5	(18.5)
Codeine[b]	25	(26.6)	19	(29.2)	5	(18.5)
Tramadol	3	(3.2)	–	–	3	(11.1)
Fentanyl	2	(2.1)	2	(3.1)	–	–
Propoxyphene	1	(1.1)	–	–	1	(3.7)

[a] 1 prescription for morphine had no indication reported
[b] 1 prescription for codeine had no indication reported
[c] 2 prescriptions did not report an indication, (n=92)

Table 8: Prevalence of prescription opioid use by geographic region in U.S. and Canada

	Region Total N= 1035	**Any Opioid Use N= 67**	**% of Region Total**
Canada[a]	76	3	(4.0)
United States	863	59	(6.8)
Pacific	247	22	(8.9)
Mountain	180	15	(8.3)
Midwest	116	5	(4.3)
South	200	9	(4.5)
Northeast	120	8	(6.7)
NA	96	5	(5.2)

[a] Data from participants in Northwestern Territories (a federal territory of Canada, not a province) were included

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